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Hepatotoxic impact of desloratadine/dihydroartemisinin /piperaquine on healthy and parasitized mice

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ABSTRACT

Background: Desloratadine/dihydroartemisinin/piperaquine (DL/D/P) can be used for malaria treatment, but its safety assessment is imperative. Objective: To evaluate its hepatotoxic effect on healthy and *Plasmodium berghei*-infected mice. Method: Fifty-four adult Swiss albino mice (25-30g) were used. The mice, n=6/group were inoculated with *Plasmodium berghei* (1×10^7) and treated with DL (5mg/kg), D/P (1.71/13.7mg/kg) and DL/D/P daily for 4 days, respectively. The healthy mice were treated with DL (5mg/kg), D/P (1.71/13.7mg/kg) and DL/D/P daily for 28 days, respectively. After drug treatment, the mice were weighed and anesthetized. Blood samples were collected and assessed for liver function indices. Liver samples were excised, weighed and evaluated for oxidative stress markers and histology. Results: DL, D/P and DL/D/P had no significant ($p>0.05$) effects on liver function parameters in parasitized mice when compared to control. DL, D/P and DL/D/P significantly decreased body weight and significantly increased liver weight in healthy mice at $p<0.05$, $p<0.05$, and $p<0.01$, respectively when compared to control. Serum aminotranferases, gamma-glutamyl transferase, lactate dehydrogenase, alkaline phosphatase and bilirubin levels increased significantly while total protein and albumin levels decreased significantly in healthy mice treated with DL ($p<0.05$), D/P($p<0.01$) and DL/D/P ($p<0.001$) when compared to control. Significantly decreased liver catalase, glutathione peroxidase superoxide dismutase, and glutathione with significantly increased malondialdehyde levels were observed in healthy mice treated with DL ($p<0.05$), D/P ($p<0.01$) and DL/D/P ($p<0.001$) when compared to control. DL/D/P produced hepatocyte necrosis in healthy mice. Conclusion: Malaria treatment with DL/D/P may be safe on the liver, but prolonged use may cause liver dysfunction.

Keywords: Dihydroartemisinin/piperaquine, Desloratadine, *Plasmodium*, Hepatotoxicity, Mice

1. INTRODUCTION

The liver is a vital organ responsible for an array of functions that aids metabolism, immunity, bile secretion, digestion, detoxification, and vitamin

storage (Karla *et al*., 2020). The liver can thus be regarded as an organ involved in sustaining and regulating homeostasis in the body. Almost all biochemical pathways to growth, energy provision, nutrient supply, and reproduction requires the liver (Sharma *et al*., 1991). The Livers anatomy and physiology enables it function in the disposition of drugs administered orally, serving as a portal to tissues and a major site of drug metabolism (Baillie and Rettie, 2011). Drug metabolism by the liver sometimes produces active and toxic metabolites which may cause hepatotoxicity (Remmer, 1970).

Hepatotoxicity associated with some antimalarial drugs has raised some notable concern (Omotuyi *et al*., 2008; Owumi *et al*., 2015; Yin el al., 2014). Studies in humans have shown elevation of liver enzymes of clinical significance (Ribeiro, and Olliaro, 1998). Severe hepatotoxicity with visible systemic signs has been reported with the use of chloroquine (Farver and Lavin, 1999; Lee, 2003, Liu, 2015). A clear correction between antimalarial drug administration and elevated liver enzymes has been observed in some artemisinin-based combination therapies (ACTs), (Moore, 2018). Halofantrine was reported to cause elevations of liver enzymes and pathologic changes in guinea pigs, such as severe hepatic degeneration (Obi *et al*., 2004).

Dihydroartemisinin-piperaquine (D/P) is part of the five ACTs currently recommended by the World Health Organization (WHO) for the treatment of uncomplicated malaria infection (Zani *et al*., 2014). Piperaquine which has a half-life of several weeks has activity against chloroquine-resistant *Plasmodium vivax* and *Plasmodium falciparum* (Hung *et al*., 2004; Tarning *et al*., 2008). Dihydroartemisinin is the active metabolite of artemether and artesunate. D/P is an effective and frequently used ACT (Gutman *et al*., 2017). It may be safe (Myint *et al*., 2007), but reports suggest it may cause hepatic dysfunction (Okafor, Ufele and Nwankwo, 2019; Batty *et al*., 2008; Mesembe *et al*., 2009). Desloratadine (DL) is a non- sedating second generation H_1- antihistamine that was established for the treatment of allergic rhinitis in 2001 (Villa, 2001), but studies showed it has potential antimalarial activity (Aneesa, 2011) and showed synergistic activity with chloroquine (Aneesa, 2011). In recent studies, DL increased the antimalarial activity of D/P in *Plasmpdium berghei*-infected mice, (Georgewill *et al*., 2021), but with a paucity of scientific information on the safety of their combination especially on the liver. Hence the present study assessed the hepatotoxic effect of combined DL and D/P on healthy and *Plasmodium berghei*-infected mice which is imperative.

2. MATERIALS AND METHODS

2.1. Animals, malaria parasite and drugs

A total of fifty-four adult Swiss albino mice (n=6/group) of both sexes (25-30g) obtained and kept at the animal house of the Department of Pharmacology, Faculty of Basic Clinical Sciences, University of Port Harcourt, Rivers State, Nigeria were used. The mice were kept in well ventilated and clean cages, maintained under standard environmental conditions and fed with standard laboratory animal food pellets with water *ad libitum*. DL (Merck & Co) and D/P (Bliss GVS Pharma Ltd, India) were used. The following doses from previous studies on the antiplasmodial activity of DL/D/P were used: D/P (1.71/13.7 mg/kg) and DL (5 mg/kg) (Georgewill *et al*., 2021). Donor mice infected with Chloroquine-sensitive strain of *Plasmodium berghei* (*P.berghei*) (NK65) provided by the Nigerian Institute of Medical Research (NIMR), Yaba, Lagos, Nigeria were used. The donor mice were sacrificed and blood samples were collected by cardiac puncture. The blood samples were diluted to 2ml with 0.9% saline containing 1×10^7parasitized erythrocytes and were used to intraperitoneally (ip) infect the experimental mice used.

2.2. Parasite inoculation, treatment and animal sacrifice

Thirty mice randomized into n=6/ group were used. The mice were grouped II-V and inoculated (i.p) with *P. berghei* containing 1×10^7parasitized erythrocytes. After 3 days, treatment commenced orally as follows: Group 1(Normal control) and group II (parasitized control) received 0.2 ml of normal saline, groups III-V received (D/P) (1.71/13.7 mg/kg), DL (5 mg/kg) and DL/D/P daily for 4 days, respectively. For the sub-acute study, twenty-four healthy mice of n=6/group of four groups were used. Group I (Control) daily received 0.2ml of normal saline orally for 28 days. Groups II-IV orally received (D/P) (1.71/13.7 mg/kg), DL (5 mg/kg) and DL/D/P daily for 28 days, respectively. After drug administration, the mice were fasted overnight, weighed and anesthetized with diethylether and blood samples were obtained by cardiac puncture. Blood samples were centrifuged at a speed of 1200 rpm for 20 minutes and sera separated and evaluated for biochemical markers. Mice were dissected and the liver harvested and rinsed in saline. The rinsed liver were homogenized in 0.1 M Tris-HCl solution buffered (pH 7.4) and centrifuged (2000 rmp for 20 minutes). The supernatants were decanted and evaluated for oxidative stress markers.

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2.3. Serum biochemical marker assessments

2.3.1 Assessments of liver biochemical markers

Serum alanine aminotransferase (ALT), total bilirubin (TB), alkaline phosphatase (ALP), aspartate aminotransferase (AST), albumin, and lactate dehydrogenase (LDH) were measured using laboratory test apparatus according to the manufacturer's specifications.

2.3.2 Evaluation of oxidative stress markers

Liver glutathione (GSH) was assayed as described by Sedlak and Lindsay (1968). Superoxide dismutase (SOD) was estimated as reported by Sun and Zigman (1978). Catalase (CAT) was measured using the procedure explained by Aebi (1984). Glutathione peroxidase (GPx) was determined as explained by Rotruck *et al*., (1973). Malondialdehyde (MDA) was measured according to the method described by Buege and Aust (1978).

2.4. Histology of the liver

Liver tissues were harvested and preserved in 10% buffered formalin for 24hr. The Liver tissues were dehydrated in graded alcohol concentrations. The tissues were processed, embedded in paraffin wax and sectioned (3 μm each). The sectioned liver tissues were stained with Eosin and Hematoxylin and examined with a light microscope.

2.5. Statistical analysis

Data were expressed as mean ± SEM. Data were subjected to one-way Analysis of Variance (ANOVA) and complemented with Tukey's multiple range test using Graph Pad Prism 5 Software (San Diego, CA USA). Statement on statistical significance was based on $p< 0.05$; $p<0.01$ and $p<0.001$.

3. RESULTS

Effects of desloratadine/dihydroartemisinin/piperaquine on body and liver weights of healthy and *Plasmodium berghei*-infected Mice

Body and liver weights were not altered ($p>0.05$) in *P. berghei*-infected mice treated with DL, D/P and DL/D/P for 4 days, respectively when compared to control (Table 1). Following 28 days of treatment, body weight significantly decreased while liver weight significantly increased in healthy mice treated with DL ($p<0.05$), D/P ($p<0.05$) and DL/D/P ($p<0.01$), respectively when compared to control (Table 1).

Table 1: Effect of desloratadine/dihydroartemisinin/piperaquine on body and liver weights of healthy and *Plasmodium berghei*-infected mice

Treatment	Final body weight (g)		Absolute liver weight (g)		Relative liver weight (%)	
	Healthy mice	Parasitized mice	Healthy mice	Parasitized mice	Healthy mice	Parasitized mice
Control	30.40±2.27	25.00±2.28	1.83±0.06	1.85±0.03	6.02±0.03	7.40±0.57
DL	25.43±2.21*	24.80±3.12	2.33±0.05*	1.83±0.07	9.16±0.65*	7.37±0.34
D/P	24.20±2.69*	24.40±2.78	2.30±0.04*	1.80±0.09	9.50±0.72*	7.38±0.02
DL/ D/ P	21.70±2.85π	23.21±3.47	2.69±0.06π	1.77±0.04	12.40±1.07π	7.63±0.06

Data as mean ± SEM, SEM: Standard error of mean. n=6, DL: Desloratadine, D/P: Dihydroartemisinin/piperaquine, * $p<0.05$, π $p<0.01$ Significant difference when compared to control (Healthy mice)

Effects of desloratadine/dihydroartemisinin/piperaquine on serum liver biochemical markers of healthy and *Plasmodium berghei*-infected mice

Serum AST, ALT, ALP, LDH, TB, total protein and albumin levels remained unchanged ($p>0.05$) in *P. berghei*-infected mice treated with DL, D/P and DL/D/P for 4 days, respectively when compared to control (Table 2). However, significant increases in serum AST, ALT, ALP, LDH, and TB levels with significant decreases in serum total protein and albumin levels were detected in healthy mice treated with DL ($p<0.05$), D/P ($p<0.01$) and DL/D/P ($p<0.001$), respectively when compared to control (Table 3). In the healthy mice, treatment with DL, D/P and DL/D/P produced no significant changes ($p>0.05$) on serum TG, CH, HDL-C, and LDL-C levels when compared to control (Table 4).

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Table 2: Effect of desloratadine/dihydroartemisinin/piperaquine on serum liver biochemical markers of *Plasmodium berghei*-infected mice

Treatment	ALT (U/L)	AST (U/L)	ALP (U/L)	LDH (U/L)	TB (g/dL)	T. Protein (g/dL)	Albumin (g/dL)
Control	30.20±2.21	38.60±4.48	27.80±4.07	33.05±3.12	3.14±0.37	5.66±0.20	4.46±0.06
PC	31.50±2.34	39.20±4.65	28.30±4.12	36.17±3.65	3.22±0.47	5.43±0.42	4.40±0.08
DL	29.60±3.15	38.70±4.35	29.20±3.07	34.50±2.12	3.37±0.53	5.38±0.32	4.37±0.12
D/P	29.80±2.57	40.40±4.57	29.60±4.28	37.50±4.32	3.35±0.31	5.32±0.67	4.34±0.05
DL/ D/ P	31.20±2.38	43.80±4.18	30.20±3.65	38.90±4.15	3.50±0.23	5.21±0.20	4.30±0.04

Data as mean± SEM, n=6, SEM: Standard error of mean, PC: Parasitized untreated control, DL: Desloratadine, D/P: Dihydroartemisinin/piperaquine, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, TB: Total bilirubin, ALP: Alkaline phosphatase, T. Protein: Total protein

Table 3: Effect of desloratadine/dihydroartemisinin/piperaquine on serum liver biomarkers of healthy mice

Treatment	ALT (U/L)	AST (U/L)	ALP (U/L)	LDH (U/L)	TB (g/dL)	T.Protein (g/dL)	Albumin (g/dL)
Control	31.73±3.03	43.80±6.27	25.6±3.21	33.10±3.17	3.12±0.32	8.30±0.12	5.34±0.45
DL	37.60±4.12*	65.70±7.04*	39.12±4.34*	60.32±4.60*	5.68±0.61	6.31±0.06*	3.71±0.09*
D/P	60.21±5.29**	89.21±6.57**	58.20±6.23**	79.20±5.31**	6.10±0.71**	6.00±0.21**	3.20±0.09**
DL/ D/ P	98.10±6.23π	163.9±8.23 π	101.20±8.03π	113.7±7.25π	8.01±0.42 π	4.50±0.84 π	2.01±0.64 π

Data as mean± SEM, n=6, SEM: Standard error of mean, DL: Desloratadine, D/P: Dihydroartemisinin/piperaquine, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, TB: Total bilirubin, ALP: Alkaline phosphatase, T. Protein: Total protein, * $p<0.05$, ** $p<0.01$ and π $p<0.001$ Significant difference when compared to control.

Table 4: Effect of desloratadine/dihydroartemisinin/piperaquine on serum lipid parameters of healthy mice

Treatment	T g/dL	CHOL g/dL	HDL-C g/dL	LDL-C g/dL
Control	51.60±5.32	87.50±8.51	31.70±3.21	28.60±3.56
DL	52.90±6.37	89.70±7.04	30.90±3.07	29.10±3.01
D/P	55.40±7.20	93.20±9.05	32.50±3.71	30.40±4.37
DL/ D/ P	57.20±7.90	97.40±9.11	34.70±3.11	31.30±4.16

Data as mean± SEM, n=6, DL: Desloratadine, D/P: Dihydroartemisinin/piperaquine, T: Triglyceride, CHOL: Total cholesterol, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol. SEM: Standard error of mean.

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Table 5: Effect of desloratadine/dihydroartemisinin/piperaquine on liver oxidative stress markers of *Plasmodium berghei*-infected mice

Treatment	MDA nmole/mg protein	GSH µmole/mg protein	CAT U/mg protein	SOD U/mg protein	GPx U/mg protein
Control	0.24±0.05	16.30±1.44	25.33±3.07	20.23±3.04	15.29±1.56
PC	0.25±0.07	16.27±0.98	25.30±2.55	20.11±2.88	15.22±1.99
DL	0.23±0.09	16.26±1.23	25.27±3.77	20.09±3.22	15.19±1.77
D/P	0.25±0.06	16.23±1.45	24.90±4.32	19.88±1.31	15.00±1.63
DL/ D/ P	0.26±0.07	16.20± 1.11	24.80±2.46	19.67±1.52	14.97±1.21

Data as mean ± SEM, SEM: Standard error of mean, PC: Parasitized untreated control, DL: Desloratadine, D/P: Dihydroartemisinin/piperaquine, MDA: Malondialdehyde, GSH: Glutathione, CAT: Catalase, SOD: Superoxide dismutase GPx: Glutathione peroxidase.

Table 6: Effect of desloratadine/dihydroartemisinin/piperaquine on liver oxidative stress markers of healthy mice

Treatment	MDA nmole/mg protein	GSH µmole/mg protein	CAT U/mg protein	SOD U/mg protein	GPx U/mg protein
Control	0.23±0.01	16.71±0.64	27.10±1.07	17.11±2.04	17.81±0.80
DL	0.37±0.03*	12.40±0.71*	22.61±3.56*	13.47±2.43*	13.90±1.02*
D/P	0.49±0.05**	8.72±0.55**	18.21±2.61**	11.23±1.53**	10.50±0.31**
DL/ D/ P	0.61±0.04 π	5.27± 0.37 π	11.70±1.35 π	7.07±2.81π	7.60±0.41 π

Data as mean ± SEM, SEM: Standard error of mean, n=6, DL: Desloratadine, D/P: Dihydroartemisinin/piperaquine, D/P/DL: MDA: Malondialdehyde, GSH: Glutathione, CAT: Catalase, SOD: Superoxide dismutase GPx: Glutathione peroxidase,* p<0.05, **p<0.01, π p<0.001 Significant difference when compared to control.

Effects of desloratadine/dihydroartemisinin/piperaquine on liver oxidative stress markers and histology of healthy mice

The activities of liver antioxidants (SOD, GSH, CAT and GPx) were normal in *P. berghei*-infected mice treated for 4 days (Table 5), but were significantly decreased in healthy mice treated with DL ($P < 0.05$), D/P ($P < 0.01$) and DL/D/P ($P < 0.001$) for 28 days when compared to control (Table 6). MDA levels were normal in *P. berghei*-infected mice treated for 4 days (Table 6), but were significantly increased in healthy mice following 28 days treatment with DL ($P < 0.05$), D/P ($P < 0.01$) and DL/D/P ($P < 0.001$) when compared to control (Table 6). The photomicrographs of the liver of the control mice showed normal hepatocytes and central vein (Figure A). The liver of DL –treated healthy mice showed central vein congestion (Figure B). The liver of D/P-treated healthy mice showed central vein congestion (Figure C). The liver of DL/D/P-treated healthy mice showed central vein congestion and hepatocyte necrosis (Figure D).

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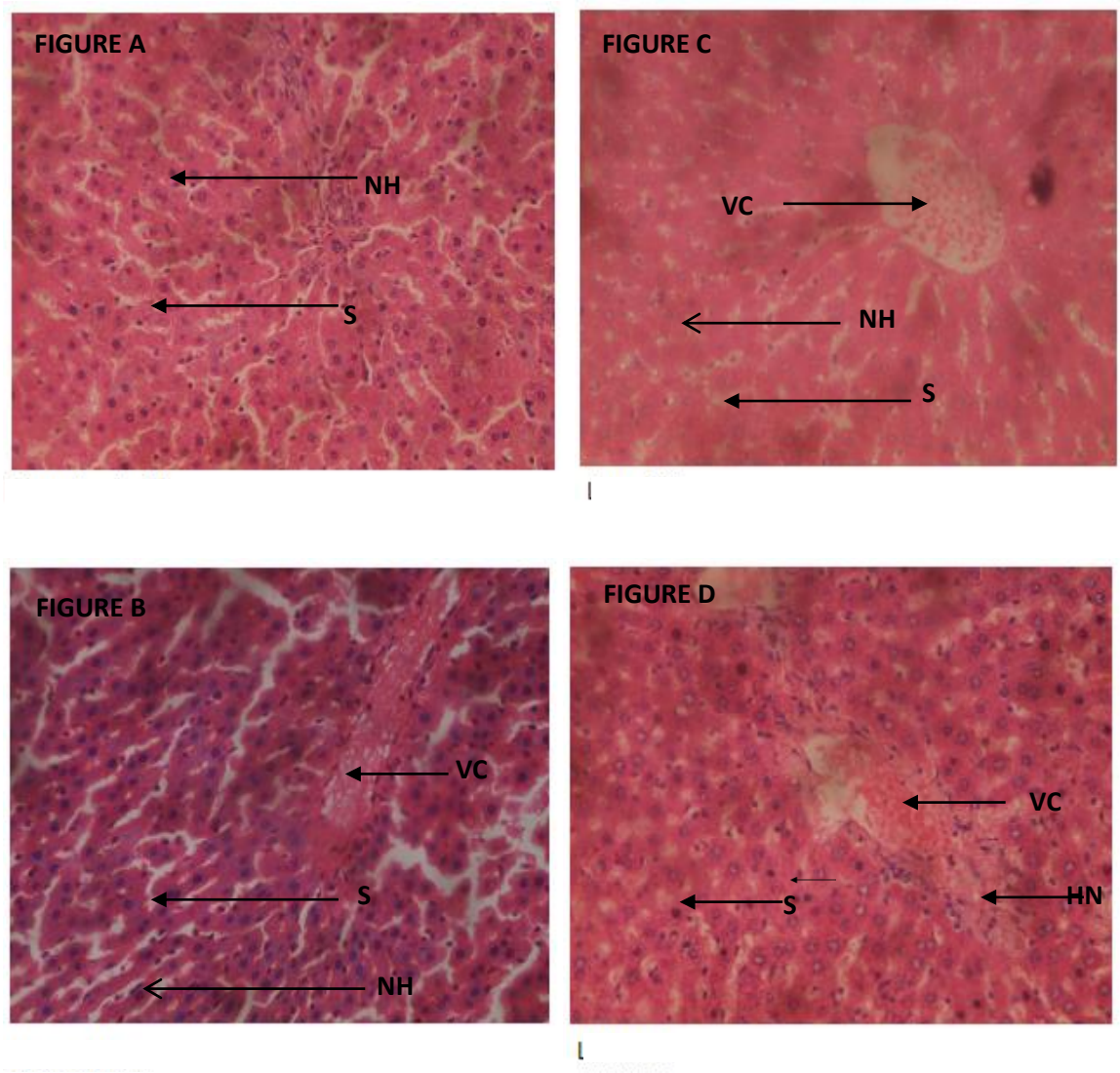

The liver of the control mice (Figure A), the liver of DL-treated healthy mice (Figure B), the liver of D/P-treated healthy mice (Figure C) and the liver of DL/D/P-treated healthy mice (Figure D) X 400. NH: Normal hepatocytes, VC: Central vein congestion HN: Hepatocyte necrosis, S: Sinusoids

4. DISCUSSION

Studies on toxicity are important steps in the development of new drugs (Parasuraman, 2011). Considering the potential antimalarial benefit of DL/D/P, comprehensive knowledge on its toxicity profile is lacking especially on the liver. The present study evaluated the hepatotoxicity of DL/D/P in healthy and *P. berghei*-infected mice. The assessment of body and organ weights in toxicity studies is an essential step in the evaluation of chemical substances (Sellers *et al*., 2007). An abnormal change in an organ weight caused by an administered xenobiotic is an indicator of its toxicity (Teo *et al*., 2002; Wang *et al*., 2007). In this present study, DL/D/P had no effects on the liver and body weights of *P. berghei* -infected mice treated for 4 days. But decreased body weight and increased liver weight occurred in healthy mice treated with DL/D/P for 28 days. In healthy mice, it implies that DL/D/P may have decreased appetite and induced inflammation in the liver of treated mice. Liver biochemical markers evaluated in this study are important and effective parameters used for the diagnoses of liver diseases (Adikwu *et al*., 2020). In this study, treatment with DL/D/P had no negative effect on serum liver biochemical markers of *P. berghei* -infected mice treated for 4 days. However, treatment of healthy mice for 28 days with DL/D/P altered serum liver biochemical markers marked by increased serum AST, ALT, ALP, TB, LDH levels and decreased total protein and albumin levels. The observation is a sign of hepatic damage (Adikwu *et al*., 2020), which may be caused by the distortion of hepatocyte membrane leading to the leakage of hepatocyte cytosolic contents (Bhattacharyya, 2003). There were no observable changes in serum T, CHL, LDL-C and HDL-C levels of DL/D/P-treated healthy rats for 28 days.

Oxidative stress is a consequence of the overproduction of ROS by metabolic reactions associated with oxygen, which alters oxidant/antioxidant balance in favour of the oxidant (Betteridge, 2000; Birben *et al*, 2012). ROS are unpaired electrons and highly reactive molecules, when in excess they react with various biological biomolecules in cells (nucleic acids, lipids, and proteins) causing functional and structural damage (Birben *et al*, 2012). In this study, liver oxidative stress makers of *P. berghei* -infected mice treated with DL/D/P were not altered. In healthy mice, DL/D/P altered liver oxidative stress markers marked by decreased antioxidants and elevated MDA level. Free radical-induced lipid peroxidation, plays an important function in pathological processes. Free radical-induced lipid peroxidation can be measured by conjugated dienes, MDA, and 4-hydroxynonenal, but MDA has been frequently used (Grotto *et al*., 2009). DL/D/P had no conspicuous effect on MDA level of *P. berghei* -infected mice treated for 4 days. In contrast, DL/D/P visibly increased MDA levels in healthy mice treated for 28 days. This indicates that DL/D/P caused hepatic lipid peroxidation in healthy mice. This may be attributed to the induction of excess ROS production in the liver by DL/D/P leading to oxidative stress. The liver of DL/D/P treated healthy mice for 28 days showed hepatic necrosis and central vein congestion. This finding could be due to liver bimolecular damage to DNA, proteins, lipids and other cellular components through oxidative stress caused by ROS production (Grotto *et al*., 2009).

5. CONCLUSION

Results from this study showed that treatment of malaria using DL/D/P may not cause hepatotoxicity except with long term use.

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Ethical approval

The Animal ethical guidelines are followed in the study for experimentation.

Conflict of Interest:

The authors declare that there are no conflicts of interests.

Data and materials availability:

All data associated with this study are present in the paper.

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